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A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management

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ABSTRACT

BACKGROUND

Obesity is a chronic disease with serious health consequences, but weight loss is difficult to maintain through lifestyle intervention alone. Liraglutide, a glucagon-like peptide-1 analogue, has been shown to have potential benefit for weight management at a once-daily dose of 3.0 mg, injected subcutaneously.

METHODS

We conducted a 56-week, double-blind trial involving 3731 patients who did not have type 2 diabetes and who had a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of at least 30 or a BMI of at least 27 if they had treated or untreated dyslipidemia or hypertension. We randomly assigned patients in a 2:1 ratio to receive once-daily subcutaneous injections of liraglutide at a dose of 3.0 mg (2487 patients) or placebo (1244 patients); both groups received counseling on lifestyle modification. The coprimary end points were the change in body weight and the proportions of patients losing at least 5% and more than 10% of their initial body weight.

RESULTS

At baseline, the mean (±SD) age of the patients was 45.1±12.0 years, the mean weight was 106.2±21.4 kg, and the mean BMI was 38.3±6.4; a total of 78.5% of the patients were women and 61.2% had prediabetes. At week 56, patients in the liraglutide group had lost a mean of 8.4±7.3 kg of body weight, and those in the placebo group had lost a mean of 2.8±6.5 kg (a difference of −5.6 kg; 95% confidence interval, −6.0 to −5.1; P<0.001, with last-observation-carried-forward imputation). A total of 63.2% of the patients in the liraglutide group as compared with 27.1% in the placebo group lost at least 5% of their body weight (P<0.001), and 33.1% and 10.6%, respectively, lost more than 10% of their body weight (P<0.001). The most frequently reported adverse events with liraglutide were mild or moderate nausea and diarrhea. Serious events occurred in 6.2% of the patients in the liraglutide group and in 5.0% of the patients in the placebo group.

CONCLUSIONS

In this study, 3.0 mg of liraglutide, as an adjunct to diet and exercise, was associated with reduced body weight and improved metabolic control. (Funded by Novo Nordisk; SCALE Obesity and Prediabetes NN8022-1839 ClinicalTrials.gov number, NCT01272219.)

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The increase in the rate of obesity, a chronic disease with serious health consequences, largely explains the recent tripling in the prevalence of type 2 diabetes.[1,2] Weight loss of 5 to 10% has been shown to reduce complications related to obesity and improve quality of life[3-7]; however, weight loss is difficult to maintain with lifestyle intervention alone.[8]

Liraglutide, a glucagon-like peptide-1 analogue with 97% homology to human glucagon-like peptide-1, is approved for the treatment of type 2 diabetes at doses up to 1.8 mg once daily.[9] Weight loss with liraglutide is dose-dependent up to 3.0 mg once daily[10,11] and is mediated by reduced appetite and energy intake rather than by increased energy expenditure.[12]

A Quick Take summary is available at NEJM.org

This 56-week, randomized, placebo-controlled trial aimed to evaluate the efficacy and safety of 3.0 mg of liraglutide, injected subcutaneously once daily, as an adjunct to a reduced-calorie diet and increased physical activity, for weight management in overweight or obese adults who did not have diabetes at baseline.

Methods

Study Overview

We conducted the study from June 1, 2011, through March 18, 2013, at 191 sites in 27 countries in Europe, North America, South America, Asia, Africa, and Australia. The trial protocol was approved by local ethics committees or institutional review boards and is available with the full text of this article at NEJM.org. The trial was conducted in accordance with the principles of the Declaration of Helsinki[13] and Good Clinical Practice guidelines.[14] A 2-year extension of the trial involving patients with prediabetes that was designed to evaluate whether liraglutide is associated with delayed onset of type 2 diabetes was recently completed. All the authors were involved in the design or conduct of the study and the preparation of the manuscript, including the decision to submit it for publication, and all attest to the accuracy and completeness of data and the data analyses. The sponsor, Novo Nordisk, planned and performed the statistical analyses, provided editorial and writing assistance, and provided the trial drugs.

Patients

The trial enrolled patients 18 years of age or older who had stable body weight and a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 30 or higher, or 27 or higher if the patient had treated or untreated dyslipidemia or hypertension (Table S1 in the Supplementary Appendix, available at NEJM.org). All the patients provided written informed consent before participation. Key exclusion criteria were type 1 or 2 diabetes, the use of medications that cause clinically significant weight gain or loss, previous bariatric surgery, a history of pancreatitis, a history of major depressive or other severe psychiatric disorders, and a family or personal history of multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma. Details of the eligibility and exclusion criteria are provided in the Supplementary Appendix.

Study Design and Treatments

Randomization was performed with the use of a telephone or Web-based system provided by the sponsor. Eligible patients were randomly assigned, in a 2:1 ratio, to receive once-daily subcutaneous injections of liraglutide, starting at a dose of 0.6 mg with weekly 0.6-mg increments to 3.0 mg, or placebo; both groups received counseling on lifestyle modification (Fig. S1 in the Supplementary Appendix). Patients were stratified according to prediabetes status at screening[15] and according to BMI (≥30 vs. <30). Patients, investigators, and the sponsor were unaware of the study-group assignments. Liraglutide and placebo were provided in FlexPen devices (Novo Nordisk). After 56 weeks, patients in the liraglutide group who did not have prediabetes at screening were randomly assigned in a 1:1 ratio to continue receiving liraglutide or to switch to placebo for 12 weeks to assess whether efficacy was maintained after discontinuation of liraglutide treatment and whether there were safety issues related to discontinuation. Patients in the placebo group continued to receive placebo.

Study Procedures and End Points

Patients were evaluated every 2 weeks until week 8; thereafter, patients were evaluated every 4 weeks until week 44 and were evaluated again

at weeks 50, 56, 58, 60, 64, 68, and 70. All patients received standardized counseling on lifestyle modification approximately monthly (see the Supplementary Appendix).[11] Patients who withdrew early were asked to return at week 56 for measurement of their weight and recording of adverse events.

The three prespecified coprimary end points, assessed at week 56, were weight change from baseline, the proportion of patients who lost at least 5% of their baseline body weight, and the proportion of patients who lost more than 10% of their baseline body weight. Secondary end points included changes from baseline in BMI, waist circumference, glycemic control variables, cardiometabolic biomarkers, and health-related quality of life. The timing of assessments is described in the Methods section in the Supplementary Appendix. Health-related quality of life was assessed with the use of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36; in which higher scores indicate better quality of life)[16] and the Impact of Weight on Quality of Life–Lite[17] (in which higher scores indicate better quality of life) and Treatment Related Impact Measure–Weight[18] (in which higher scores indicate better quality of life) questionnaires. The proportion of patients who modified their use of lipid-lowering or antihypertensive medications was also assessed. Additional methods are described in the Supplementary Appendix.

Specific attention was given to types of adverse events that have an increased prevalence among obese persons or that were relevant to the drug class of liraglutide: of 17 types of adverse events, 9 were prospectively assessed by independent medical experts who were unaware of the study-group assignments (Table S2 in the Supplementary Appendix). We report adverse events that occurred during the main 56-week trial period, with onset on or after the first day of treatment and no later than 14 days after the last day of treatment, unless otherwise stated.

STATISTICAL ANALYSIS

We estimated that with a sample size of 2400 patients assigned to receive liraglutide and 1200 assigned to receive placebo, the study would have more than 99% power to detect a between-group difference in the three coprimary efficacy end points of the main 56-week trial and in the primary end point of the 2-year extension. The power for the first coprimary end point, weight change, was calculated with the use of a two-sided Student's t-test at a 5% significance level. The power for the two categorical coprimary end points was calculated with the use of a two-sided chi-square test, also at a 5% significance level (see the Supplementary Appendix).

The prespecified efficacy analyses used data from the full-analysis set, which included all patients who underwent randomization and received at least one dose of a study drug and had at least one assessment after baseline. The safety-analysis set included all patients who were randomly assigned to a study group and had exposure to a study drug. Missing values were imputed with the use of the last-observation-carried-forward method for measurements made after baseline. For weight, only fasting measurements were used. The three coprimary end points were analyzed in hierarchical order. An analysis of covariance model was used to analyze mean changes in continuous end points. The model included treatment, country, sex, BMI stratification, status with respect to prediabetes at screening, and interaction between BMI strata and prediabetes status as fixed effects, with the baseline value of the relevant variable as a covariate. Categorical changes for dichotomous end points were analyzed with the use of logistic regression with the same fixed effects and covariates as the respective analysis of covariance. Sensitivity analyses, performed to assess the robustness of the primary analyses, included repeated-measures and multiple-imputation analyses, which used a model-based approach for missing data (see the Supplementary Appendix). A total of 63 prespecified subgroup analyses were performed to investigate whether prediabetes status had any effect on the primary and secondary end points and whether baseline BMI (in four categories) had any effect on weight or glycated hemoglobin level (see the Methods in the Supplementary Appendix). Results are presented only if an effect was shown.

RESULTS

TRIAL POPULATION

A total of 3731 patients underwent randomization: 2487 to lifestyle intervention plus liraglu-

tide, at a dose of 3.0 mg once daily, and 1244 to lifestyle intervention plus placebo. The baseline characteristics were similar in the two groups (Table 1, and Tables S3 and S4 in the Supplementary Appendix). A total of 1789 patients (71.9%) in the liraglutide group, as compared with 801 patients (64.4%) in the placebo group, completed 56 weeks of treatment (Fig. S2 in the Supplementary Appendix). A larger percentage of patients in the liraglutide group than in the placebo group withdrew from the trial owing to adverse events (9.9% [246 of 2487 patients] vs. 3.8% [47 of 1244]); a smaller percentage of patients in the liraglutide group withdrew from the trial owing to ineffective therapy (0.9% [23 of 2487] vs. 2.9% [36 of 1244]) or withdrew their consent (10.6% [264 of 2487] vs. 20.0% [249 of 1244]).

BODY WEIGHT

After 56 weeks, patients in the liraglutide group had lost a mean (±SD) of 8.0±6.7% (8.4±7.3 kg) of their body weight, whereas patients in the placebo group had lost a mean of 2.6±5.7% (2.8±6.5 kg) of their body weight (Table 2). Weight loss with liraglutide was maintained over 56 weeks and was similar regardless of prediabetes status (Fig. 1A). A greater proportion of patients in the liraglutide group than in the placebo group lost at least 5% of their body weight (63.2% vs. 27.1%), more than 10% of their body weight (33.1% vs. 10.6%), and more than 15% of their body weight (14.4% vs. 3.5%) (Fig. 1B). Overall, approximately 92% of the patients in the liraglutide group and approximately 65% of the patients in the placebo group lost weight (Fig. 1C). The liraglutide group also had a greater reduction than the placebo group in mean waist circumference and BMI (Table 2).

Several sensitivity analyses confirmed the superiority of liraglutide over placebo with respect to the coprimary end points (Table S6 in the Supplementary Appendix). Liraglutide appeared to be less effective in patients with a mean BMI of 40 or higher than in patients with a lower BMI (Fig. S4 in the Supplementary Appendix). Estimated mean changes in body weight and secondary end points are presented in Tables S6 and S8 in the Supplementary Appendix.

GLYCEMIC CONTROL

There was a greater reduction in glycated hemoglobin, fasting glucose, and fasting insulin levels in the liraglutide group than in the placebo group (Table 2). Liraglutide was also associated with a lowering of plasma glucose levels (Fig. 2A) and higher insulin and C-peptide levels relative to placebo during an oral glucose-tolerance test (Fig. S3 in the Supplementary Appendix). The effects of liraglutide on glycated hemoglobin, fasting glucose, and glucose levels during the oral glucose-tolerance test were greater in patients with prediabetes than in those without ($P<0.001$) (Table S9 in the Supplementary Appendix). Measures of insulin resistance and beta-cell function also showed improvement with liraglutide as compared with placebo (Table S10 in the Supplementary Appendix).

The prevalence of prediabetes was significantly lower in the liraglutide group than in the placebo group at week 56 (Fig. 2B), a finding that was consistent with the improvement in glycemic control with liraglutide. Type 2 diabetes developed in more patients in the placebo group than in the liraglutide group during the course of treatment.

CARDIOMETABOLIC VARIABLES

Systolic and diastolic blood pressure decreased more in the liraglutide group than in the placebo group by week 56 (Table 2). All measures of fasting lipid levels (Table 2), as well as levels of high-sensitivity C-reactive protein, plasminogen activator inhibitor-1, and adiponectin (Table S8 in the Supplementary Appendix), showed greater improvement in the liraglutide group than in the placebo group.

HEALTH-RELATED QUALITY OF LIFE

Liraglutide treatment was associated with higher scores on the SF-36 for overall physical and mental health, a higher total score (indicating better quality of life) on the Impact of Weight on Quality of Life–Lite questionnaire (Table S7 in the Supplementary Appendix), and more favorable individual domain scores on both instruments (Fig. S5 in the Supplementary Appendix) than was placebo. The total score and the scores for weight management and treatment burden on the Treatment Related Impact Measure–Weight

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Liraglutide (N = 2487)	Placebo (N = 1244)
Sex — no. (%)		
Female	1957 (78.7)	971 (78.1)
Male	530 (21.3)	273 (21.9)
Age — yr	45.2±12.1	45.0±12.0
Race or ethnic group — no. (%)†		
White	2107 (84.7)	1061 (85.3)
Black	242 (9.7)	114 (9.2)
Asian	90 (3.6)	46 (3.7)
American Indian or Alaska Native	5 (0.2)	4 (0.3)
Native Hawaiian or other Pacific Islander	2 (<0.1)	2 (0.2)
Other	41 (1.6)	17 (1.4)
Hispanic or Latino ethnic group†	259 (10.4)	134 (10.8)
Weight — kg	106.2±21.2	106.2±21.7
Body-mass index‡	38.3±6.4	38.3±6.3
Body-mass index categories — no. (%)‡		
27–29.9: overweight	66 (2.7)	44 (3.5)
30–34.9: obese class I	806 (32.4)	388 (31.2)
35–39.9: obese class II	787 (31.6)	398 (32.0)
≥40: obese class III	828 (33.3)	414 (33.3)
Waist circumference — cm	115.0±14.4	114.5±14.3
Glycated hemoglobin — %	5.6±0.4	5.6±0.4
Fasting glucose — mg/dl	95.9±10.6	95.5±9.8
Fasting insulin — μIU/ml§	16.3±79.8	16.1±89.3
Blood pressure — mm Hg		
Systolic	123.0±12.9	123.2±12.8
Diastolic	78.7±8.6	78.9±8.5
Cholesterol — mg/dl		
Total	193.7±19.1	194.3±18.8
LDL	111.6±27.9	112.2±27.6
HDL	51.4±26.2	51.0±26.4
VLDL	25.1±49.6	25.7±49.4
Free fatty acids — mmol/liter	0.45±40.5	0.46±39.7
Triglycerides — mg/dl	126.2±56.9	128.9±61.0
Prediabetes — no. (%)¶	1528 (61.4)	757 (60.9)
Dyslipidemia — no. (%)‖	737 (29.6)	359 (28.9)
Hypertension — no. (%)‖	850 (34.2)	446 (35.9)

* Plus–minus values are observed means ±SD. For fasting insulin and lipid levels, plus–minus values are geometric means and coefficients of variation. There were no statistically significant differences between the two groups for any characteristic. To convert values for glucose to millimoles per liter, multiply by 0.05551. To convert values for cholesterol to millimoles per liter, multiply by 0.0259. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, and VLDL very-low-density lipoprotein.
† Race and ethnic group were self-reported. Patients from France did not report race or ethnic group.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The reference range is 3.0 to 25.0 μIU/mL for both sexes and all ages.
¶ Prediabetes was defined according to American Diabetes Association 2010 criteria.[15]
‖ The diagnoses of dyslipidemia and hypertension were based on self-reported medical history.

Table 2. Changes in Coprimary End Points and Cardiometabolic Risk Factors between Baseline and Week 56.*

End Point	Liraglutide (N=2437)	Placebo (N=1225)	Estimated Treatment Difference, Liraglutide vs. Placebo (95% CI)†	P Value
Coprimary end points				
Change in body weight				
% of body weight	−8.0±6.7	−2.6±5.7	−5.4 (−5.8 to −5.0)	<0.001
Kilograms of body weight	−8.4±7.3	−2.8±6.5	−5.6 (−6.0 to −5.1)	<0.001
Loss of ≥5% body weight (%)‡	63.2	27.1	4.8 (4.1 to 5.6)	<0.001
Loss of >10% body weight (%)‡	33.1	10.6	4.3 (3.5 to 5.3)	<0.001
Body weight-related end points				
Body-mass index	−3.0±2.6	−1.0±2.3	−2.0 (−2.2 to −1.9)	<0.001
Waist circumference (cm)	−8.2±7.3	−3.9±6.6	−4.2 (−4.7 to −3.7)	<0.001
Glycemic control variables				
Glycated hemoglobin (%)	−0.30±0.28	−0.06±0.30	−0.23 (−0.25 to −0.21)	<0.001
Fasting glucose (mg/dl)	−7.1±10.8	0.1±10.4	−6.9 (−7.5 to −6.3)	<0.001
Fasting insulin (%)	−12.6	−4.4	−8 (−12 to −5)	<0.001
Fasting C-peptide (%)	−8.9	−7.9	−1 (−3 to 2)	0.51
Vital signs				
Systolic blood pressure (mm Hg)	−4.2±12.2	−1.5±12.4	−2.8 (−3.56 to −2.09)	<0.001
Diastolic blood pressure (mm Hg)	−2.6±8.7	−1.9±8.7	−0.9 (−1.41 to −0.37)	<0.001
Pulse (beats/min)	2.5±9.8	0.1±9.5	2.4 (1.9 to 3.0)	<0.001
Fasting lipid profile				
Cholesterol (%)				
Total	−3.1	−1.0	−2.3 (−3.3 to −1.3)	<0.001
LDL	−3.0	−1.0	−2.4 (−4.0 to −0.9)	0.002
HDL	2.3	0.7	1.9 (0.7 to 3.0)	0.001
VLDL	−13.1	−5.5	−9.1 (−11.4 to −6.8)	<0.001
Non-HDL	−5.1	−1.8	−3.9 (−5.2 to −2.5)	<0.001
Triglycerides	−13.3	−5.5	−9.3 (−11.5 to −7.0)	<0.001
Free fatty acids	1.7	3.5	−4.2 (−7.3 to −0.9)	0.01

* Plus–minus values are observed means ±SD. For fasting insulin, fasting C-peptide, and fasting lipids, the relative change from baseline is presented. Post hoc analysis was performed for non-HDL cholesterol.

† Estimated treatment differences are from an analysis of covariance with data from the full-analysis set, with last-observation-carried-forward (LOCF) imputation. The full-analysis set comprised patients who underwent randomization, were exposed to at least one treatment dose, and had at least one assessment after baseline (69 patients were excluded from the full-analysis set: 61 owing to lack of an assessment and 8 owing to no exposure). Data on pulse are based on the safety-analysis set, which included all patients who were randomly assigned to a study group and had exposure to a study drug. Data for fasting insulin, fasting C-peptide, and fasting lipids were log-transformed for analysis and are presented as relative treatment differences.

‡ Loss of at least 5% and more than 10% of body weight were analyzed by logistic regression with data from the full-analysis set, with LOCF imputation, and are presented as the proportions of patients (%) and odds ratios.

questionnaire were also higher in the liraglutide group than in the placebo group, although the liraglutide group had a lower score for the experience of side effects.

SIDE EFFECTS AND ADVERSE EVENTS

Among patients in the safety-analysis set, the most common side effects in the liraglutide group were related to the gastrointestinal system

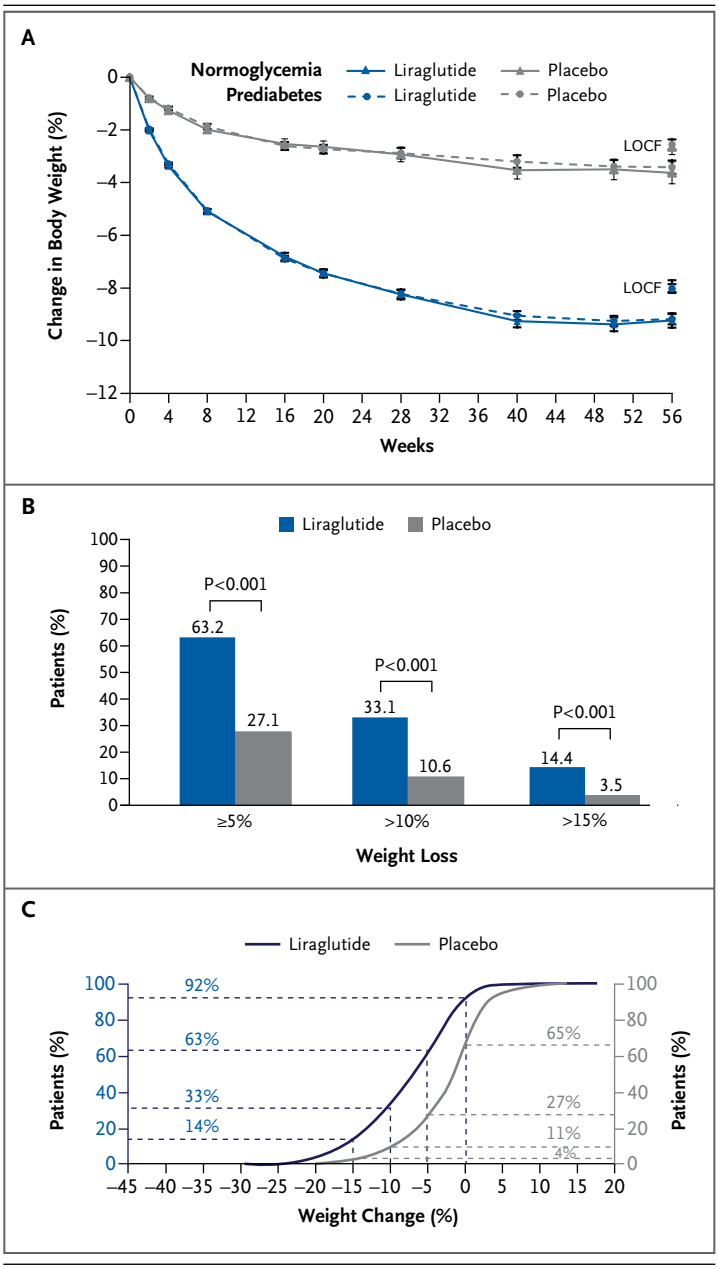

Figure 1. Liraglutide and Body Weight.

Panel A shows the mean body weight for patients in the full-analysis set who completed each scheduled visit, according to presence or absence of prediabetes at screening. I bars indicate standard error, and the separate symbols above the curves represent the 56-week weight change using last-observation-carried-forward (LOCF) imputation. The full-analysis set comprised patients who underwent randomization, were exposed to at least one treatment dose, and had at least one assessment after baseline (69 patients were excluded from the full-analysis set: 61 owing to lack of an assessment and 8 owing to no exposure). Panel B shows the proportions of patients who lost at least 5%, more than 10%, and more than 15% of their baseline body weight. Data shown are the observed means for the full-analysis set (with LOCF). Findings from logistic-regression analysis showed an odds ratio of 4.8 (95% confidence interval [CI], 4.1 to 5.6) for at least 5% weight loss and an odds ratio of 4.3 (95% CI, 3.5 to 5.3) for more than 10% weight loss; the analysis of more than 15% weight loss was performed post hoc (odds ratio, 4.9 [95% CI, 3.5 to 6.7]). Panel C shows the cumulative percentage of patients with those changes in body weight after 56 weeks of treatment.

(Table 3); 94% or more were of mild or moderate severity. Gastrointestinal events were also the most common reason that patients in the liraglutide group withdrew from the trial (159 of 2481 patients [6.4%], as compared with 9 of 1242 patients [0.7%] in the placebo group) (Fig. S6 in the Supplementary Appendix). Nausea (Fig. S7 in the Supplementary Appendix) and vomiting occurred primarily within the first 4 to 8 weeks after initiation of liraglutide treatment. The incidence of serious adverse events was higher in the liraglutide group than in the placebo group (Table 3). Three patients died — 1 in the liraglutide group (with death due to cardiomegaly and hypertensive heart disease) and 2 in the placebo group (one death each from pulmonary fibrosis and cardiorespiratory arrest).

Gallbladder-related events were more common in the liraglutide group than in the placebo group (occurring in 61 of 2481 patients [2.5%], 3.1 events per 100 patient-years of exposure; vs. 12 of 1242 patients [1.0%], 1.4 events per 100 patient-years of exposure), including more cases of cholelithiasis and cholecystitis in the liraglutide group. Most patients who reported cholelithiasis or cholecystitis underwent an elective cholecystectomy (40 of 51 patients [78%] in the liraglutide group and 6 of 8 patients [75%] in the placebo group), and most recovered and continued their assigned course of treatment or had treatment reintroduced after surgery (43 of 51 patients [84%] in the liraglutide group and 6 of 8 patients [75%] in the placebo group). The weight loss among patients with gallbladder-related adverse events was greater than the mean weight loss in the total population (Fig. S8 in the Supplementary Appendix).

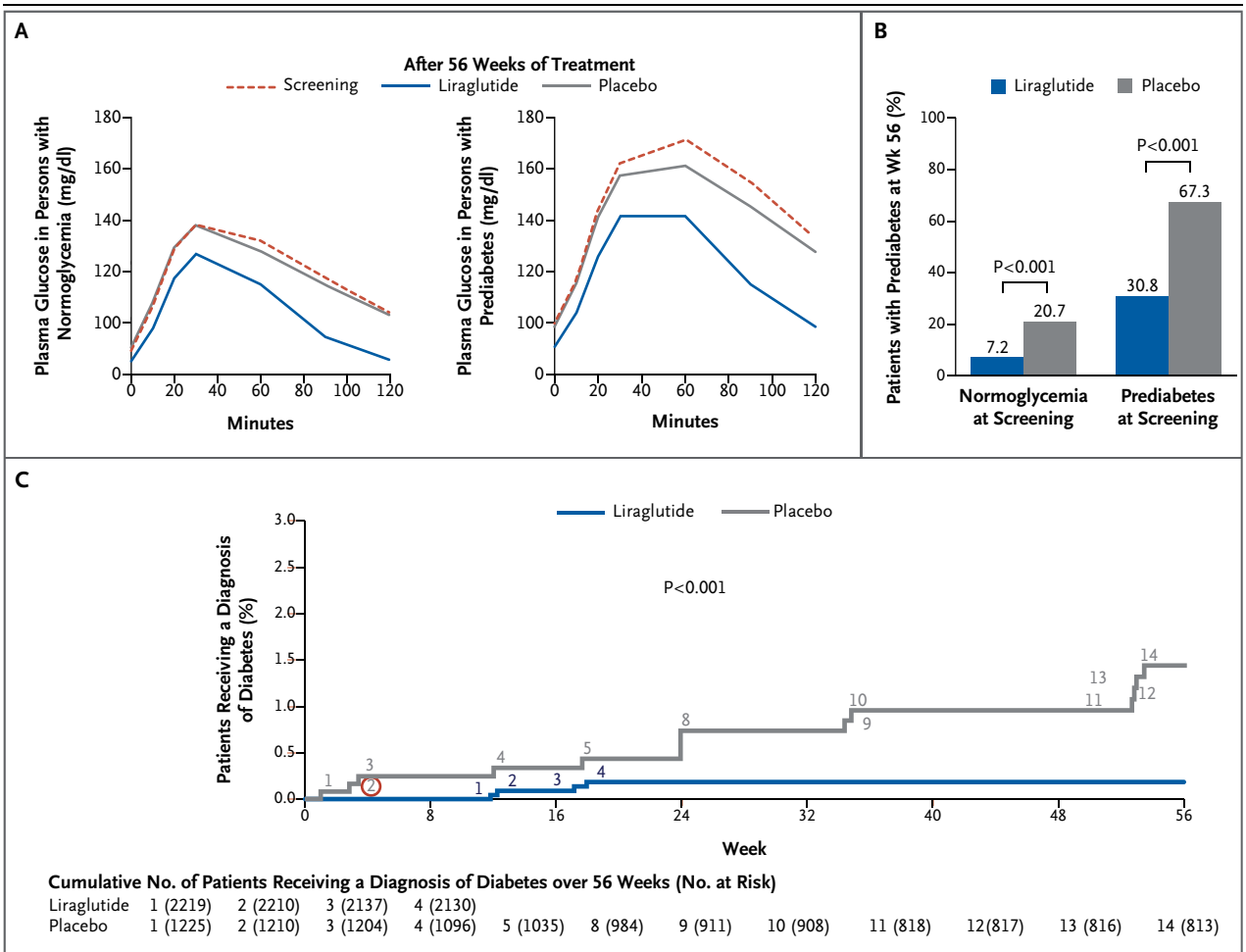

Figure 2. Liraglutide and Glucose Levels during Oral Glucose-Tolerance Test and Glycemic Status.

Panel A shows the mean plasma glucose levels during a 75-g oral glucose-tolerance test (OGTT), according to prediabetes status at screening in the full-analysis set. The OGTT was performed at screening for the diagnosis of prediabetes and again after 56 weeks of assigned treatment (see the Methods section in the Supplementary Appendix). To convert the values for glucose to millimoles per liter, multiply by 0.05551. Panel B shows the prediabetes status after 56 weeks in patients who had normoglycemia and in those who had prediabetes at screening. Findings from logistic-regression analysis showed an odds ratio for prediabetes at week 56 of 3.3 (95% confidence interval [CI], 2.4 to 4.7) among patients with normoglycemia at screening and 4.9 (95% CI, 4.0 to 5.9) among patients with prediabetes at screening. In Panels A and B, data shown are the observed means for the full-analysis set (with last-observation-carried-forward imputation). Panel C shows Kaplan-Meier estimates of the proportion of patients who received a diagnosis of type 2 diabetes during the course of the 56-week main trial period. Findings from logistic-regression analysis showed an odds ratio for development of diabetes of 8.1 (95% CI, 2.6 to 25.3). The prediabetes definition includes patients with transient and confirmed type 2 diabetes. In Panel C, all patients in whom diabetes had developed had prediabetes at screening, except for one patient in the placebo group (indicated by a red circle), who had normoglycemia. The numbers along the graphs show the cumulative number of patients who received a diagnosis of diabetes over the course of 56 weeks. The numbers of patients at risk (i.e., remaining in the trial) are shown in the table beneath the x axis.

The rates of adverse events of pancreatitis (Table S11 in the Supplementary Appendix) and neoplasms were calculated in terms of 100 patient-years at risk, covering the period from the start of treatment until the final contact with the patient (including events that occurred during the second randomized period after the end of the 56-week main study and those that occurred 15 days or more after the last day the study drug was received). Overall, 11 cases of pancreatitis were confirmed by adjudication; these cases occurred in 10 of 2481 patients in the liraglutide

Table 3. Adverse Events and Serious Adverse Events.*

Event	Liraglutide (N=2481)			Placebo (N=1242)		
	No. of Patients (%)	No. of Events	Event Rate per 100 Exposure-Years	No. of Patients (%)	No. of Events	Event Rate per 100 Exposure-Years
Adverse events in ≥5% of patients	1992 (80.3)	7191	321.8	786 (63.3)	2068	193.7
Nausea	997 (40.2)	1429	63.9	183 (14.7)	223	20.9
Diarrhea	518 (20.9)	754	33.7	115 (9.3)	142	13.3
Constipation	495 (20.0)	593	26.5	108 (8.7)	121	11.3
Vomiting	404 (16.3)	597	26.7	51 (4.1)	62	5.8
Dyspepsia	236 (9.5)	282	12.6	39 (3.1)	44	4.1
Upper abdominal pain	141 (5.7)	171	7.7	43 (3.5)	49	4.6
Abdominal pain	130 (5.2)	163	7.3	43 (3.5)	53	5.0
Nasopharyngitis	427 (17.2)	586	26.2	234 (18.8)	302	28.3
Upper respiratory tract infection	213 (8.6)	247	11.1	122 (9.8)	149	14.0
Sinusitis	128 (5.2)	141	6.3	73 (5.9)	95	8.9
Influenza	144 (5.8)	170	7.6	66 (5.3)	84	7.9
Headache	327 (13.2)	441	19.7	154 (12.4)	220	20.6
Dizziness	167 (6.7)	203	9.1	60 (4.8)	65	6.1
Decreased appetite	267 (10.8)	283	12.7	38 (3.1)	39	3.7
Back pain	171 (6.9)	210	9.4	105 (8.5)	121	11.3
Arthralgia	125 (5.0)	133	6.0	71 (5.7)	80	7.5
Fatigue	185 (7.5)	203	9.1	65 (5.2)	72	6.7
Injection-site hematoma	142 (5.7)	154	6.9	93 (7.5)	101	9.5
Serious adverse events in ≥0.2% of patients	154 (6.2)	194	8.7	62 (5.0)	75	7.0
Cholelithiasis	20 (0.8)	20	0.9	5 (0.4)	5	0.5
Cholecystitis acute	12 (0.5)	12	0.5	0	0	0.0
Osteoarthritis	6 (0.2)	7	0.3	0	0	0.0
Intervertebral disc protrusion	5 (0.2)	5	0.2	1 (0.1)	1	0.1
Pancreatitis acute†	4 (0.2)	4	0.2	0	0	0.0
Cholecystitis	4 (0.2)	4	0.2	0	0	0.0
Breast cancer	4 (0.2)	4	0.2	1 (0.1)	1	0.1
Back pain	2 (0.1)	2	<0.1	2 (0.2)	2	0.2
Uterine leiomyoma	1 (<0.1)	1	<0.1	2 (0.2)	2	0.2
Cellulitis	1 (<0.1)	1	<0.1	3 (0.2)	3	0.3
Gastroesophageal reflux disease	0	0	0.0	2 (0.2)	2	0.2
Bronchitis	0	0	0.0	2 (0.2)	2	0.2
Bladder prolapse	0	0	0.0	2 (0.2)	2	0.2
Chest pain	0	0	0.0	3 (0.2)	3	0.3

* Adverse events and serious adverse events that occurred up to and including week 58 among patients in the safety-analysis set are included and are presented by their preferred terms from the Medical Dictionary for Regulatory Activities. Events are included if they had an onset date on or after the first day the study drug was administered and no later than 14 days after the last day the study drug was administered.

† "Pancreatitis acute" was reported as serious by the investigator but was classified as mild according to revised Atlanta classification of acute pancreatitis.[19]

group (0.4%; 0.4 events per 100 patient-years at risk), of whom 9 had cases graded as mild,[19] and in 1 of 1242 patients in the placebo group (<0.1%; <0.1 events per 100 patient-years at risk). Six patients (5 of whom were in the liraglutide group) had gallstone-related pancreatitis, which was indicated by the presence of gallstones on imaging, alanine aminotransferase levels that were 3 or more times the upper limit of the normal range, or both.[20] Increases from baseline to week 56 in mean lipase and amylase activity (12.0 and 3.7 U per liter, respectively) were observed in the liraglutide group, but few patients had a lipase value that was 3 or more times the upper limit of the normal range (62 of 2447 patients [2.5%] in the liraglutide group and 13 of 1220 patients [1.1%] in the placebo group) or an amylase value that was 3 or more times the upper limit of the normal range (5 of 2447 patients [0.2%] in the liraglutide group and 1 of 1220 patients [<0.1%] in the placebo group) at any time during the trial. The positive predictive value of isolated enzyme elevations for diagnosing pancreatitis was low (<1% for a lipase value ≥3 times the upper limit of the normal range; there were no amylase values ≥3 times the upper limit of the normal range among patients who reported pancreatitis).

The mean resting pulse was increased in the liraglutide group by the end of the trial (Table 2). Additional data on vital signs are provided in the Safety Results section in the Supplementary Appendix. Prespecified cardiovascular events (Table S2 in the Supplementary Appendix) occurred in 217 of 2481 patients in the liraglutide group (8.7%; 11.9 events per 100 patient-years of exposure) and in 123 of 1242 patients in the placebo group (9.9%; 14.2 events per 100 patient-years of exposure). The rates of cardiac arrhythmia were similar in the two study groups, although the event rate for tachycardia was higher in the liraglutide group than in the placebo group (0.6 events per 100 patient-years of exposure vs. 0.1 events per 100 patient-years of exposure; all but 1 event in the liraglutide group were nonserious). Two nonfatal myocardial infarctions and one death from cardiovascular causes occurred in the liraglutide group, as compared with one nonfatal myocardial infarction, one nonfatal stroke, and one death from cardiovascular causes in the placebo group.

The incidence of adjudicated and confirmed neoplasms was similar in the liraglutide group and the placebo group (1.9 per 100 patient-years at risk and 2.4 events per 100 patient-years at risk, respectively). A numerical imbalance was observed in the incidence of malignant and premalignant breast neoplasms: 10 events in nine women in the liraglutide group versus 3 events in three women in the placebo group. Most women with events had above-average weight loss (see the Safety Results section in the Supplementary Appendix). There were no cases of medullary thyroid carcinoma or C-cell hyperplasia, and liraglutide treatment did not increase serum calcitonin concentrations.

No clinically relevant between-group differences were observed with respect to mental health assessments, including adverse events related to psychiatric disorders and questionnaire-based depression or suicidal behavior scores (see the Safety Results section in the Supplementary Appendix).

Spontaneous hypoglycemia was reported by 32 of 2481 patients (1.3%) in the liraglutide group and by 13 of 1242 patients (1.0%) in the placebo group (see the Safety Results section in the Supplementary Appendix); no events were serious or required third-party assistance.[21]

Data on changes in the use of antihypertensive and lipid-lowering medications and additional safety information are provided in the Safety Results section in the Supplementary Appendix, and results from the second randomized period after the end of the 56-week main study are shown in Table S19 in the Supplementary Appendix. No adverse effects with respect to safety variables or cases of binge eating were observed in association with treatment cessation.

DISCUSSION

Liraglutide at a once-daily dose of 3.0 mg, when used as an adjunct to a reduced-calorie diet and increased physical activity, was associated with increased weight loss in overweight and obese adults who did not have diabetes, a finding that confirms the findings in previous trials.[10,11] Liraglutide was shown to be superior to placebo with respect to all three coprimary end points. The treatment effect was similar in patients with prediabetes and those without prediabetes and was similar across baseline BMI categories. The mean change in body weight with liraglutide was –8.0±6.7% (–8.4±7.3 kg) and was generally maintained over the course of the 56-week main study period, as long as the patients continued treatment.

Liraglutide treatment was associated with reductions in cardiometabolic risk factors, including waist circumference, blood pressure, and inflammatory markers. Modest improvements in fasting lipid levels were also observed, although the clinical relevance of these improvements is uncertain. Furthermore, patients in the liraglutide group had greater reductions in fasting and postprandial glycemic variables and more improvement with respect to beta-cell function and insulin sensitivity than did the placebo group. The combination of weight loss and improved glycemic control probably contributed to the observed reductions in the prevalence of prediabetes and the delayed onset of type 2 diabetes. There were improvements in health-related quality of life, notably physical function, with liraglutide, as compared with placebo.

The safety profile of liraglutide was consistent with findings in previous reports.[9-11,22,23] Gastrointestinal disorders are common and mostly transient side effects of treatment.[23] Gallbladder-related events were more common with liraglutide than with placebo; patients with such events had above-average weight loss, which is consistent with the known risk of gallstones in association with weight loss.[24] Other mechanisms may be involved.[25] In the current trial, half the pancreatitis cases in the liraglutide group were associated with gallstones, and elevations of pancreatic enzymes were not predictive. The lack of a treatment effect on calcitonin concentration and the absence of C-cell hyperplasia or medullary thyroid carcinoma events are consistent with the prior observation that liraglutide exposure is not associated with medullary thyroid carcinoma in humans.[26] The reason for the numerical imbalance in breast neoplasms that we observed is unclear; whether there was enhanced ascertainment related to greater weight loss is unknown.

The clinical relevance of increased resting pulse with liraglutide is unknown but is probably related to the drug class.[27] The presence of glucagon-like peptide-1 receptors on the sinoatrial node suggests a direct chronotropic effect.[28] No increase in the number of serious cardiovascular events was observed in the liraglutide group, and beneficial effects of liraglutide were seen with respect to blood pressure and other cardiometabolic variables.

Limitations of the trial include the use of last-observation-carried-forward imputation in the prespecified primary analyses.[29] However, the robustness of the primary analyses was confirmed in sensitivity analyses with the use of alternative imputation methods to account for patients who withdrew from the trial. Furthermore, no correction for multiple testing was performed for secondary end points. Strengths of the trial include the large sample size, the independent blinded adjudication of specific adverse events, low attrition rates as compared with other weight-loss trials,[30-32] and a lifestyle intervention with resultant weight loss.

In conclusion, 3.0 mg of once-daily subcutaneous liraglutide, as an adjunct to diet and exercise, was associated with clinically meaningful weight loss in overweight or obese patients, with concurrent reductions in glycemic variables and multiple cardiometabolic risk factors, as well as improvements in health-related quality of life.

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